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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,662	VANDEKERCKHOVE ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *4* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2008 and 17 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☒ Claim(s) *3 and 5-7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 March 2005 and 22 February 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/25/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment, filed 2/22/08 and the corrected Reply of 4/17/08 are acknowledged and have been entered. Claims 1-7 were amended. Claims 8-12 were canceled. Accordingly, claims 1-7 are currently pending and subject to examination below.

Objections/ Rejections Withdrawn

2. The objection to and rejections of claim 8 are moot in light of the claim's cancellation.

3. Objections to the specification not reiterated below have been withdrawn.

4. The objection to claim 1 has been obviated by Applicant's amendments thereto.

5. The rejections under § 112, 2nd paragraph not reiterated below have been withdrawn.

6. The rejection of claims 2 and 6 under § 102(b) as being anticipated by Cruickshank et al. is withdrawn in response to Applicant's amendments rewriting the claims with the limitations of previous claims 3 and 7, respectively.

7. The rejection of claims 3 and 5 under § 102(b) as being anticipated by Creighton et al. is withdrawn in response to Applicant's amendments rewriting the claims with the limitations of previous claims 4 and 6, respectively.

8. The rejections of claim 5 under § 103(a) as being unpatentable over Cruickshank et al., or in the alternative as being unpatentable over Cruickshank et al. in view of Aebersold et al. and Johansson et al. have been withdrawn in favor of the rejection of the claim under § 102(b) over Cruickshank et al. in response to Applicant's amendments to rewrite the claim with the limitation of previous claim 6.

9. Similarly, the rejection of claim 4 under § 103(a) as being unpatentable over Creighton in view of Aebersold et al. is withdrawn in favor of the rejection of the claim under § 102(b) over Creighton in response to Applicant's amendments rewriting the claim with the limitation of previous claim 5.

Information Disclosure Statement

10. Applicant's Information Disclosure Statement filed 2/28/08 has been received and entered into the application. The references therein have been considered by the examiner as indicated on the attached form PTO-1449.

Specification

11. The disclosure is objected to because the application is not in compliance with the sequence rules. See the attached *Notice to Comply*.

Claim Objections

12. Claim 3 and 5-7 are objected to because of the following informalities:

13. Claim 3 recites "said complex protein mixture" in line 2, which is apparently referring back to the "complex mixture of proteins" that is recited in claim 2. Applicant is requested to employ consistent terminology, i.e., to also recite said "complex mixture of proteins" in claim 3.

14. Claim 5 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n).

15. Claim 5 recites the limitation "the targets". Applicant apparently intends to refer to the "at least one target molecule" recited in claim 1. However, the claims do not refer to "targets" *per se*, such that the reference to "the targets" is unclear and cause confusion. Consistent terminology when referring to elements earlier recited is needed in order to make Applicant's intended meaning clear.

16. Claim 6 refers to "said target molecules". Applicant apparently intends to refer to the "at least one target molecule" recited in claim 1. However, the claims do not previously refer to "target molecules" in the plural, which may cause confusion. Consistent terminology when referring to elements earlier recited is needed in order to make Applicant's intended meaning clear.

17. Claim 7 is objected to because "the mass of the peptides" should apparently read --the masses of the peptides-- for proper subject-verb agreement.

18. Claim 7 recites "the target peptides"; however, the claims do not previously recite such a term. Applicant apparently intends to refer back to the "peptides" that are recited in claim 6. Consistent terminology is needed when referring to elements earlier recited in order to make Applicant's intended meaning clear.

Claim Rejections - 35 USC § 112

19. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

20. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

21. Claim 1 recites a method to isolate "at least one target molecule **of a compound**" (emphasis added). This language is vague and indefinite because it does not make clear the relationship of the target molecule to the compound—is the target molecule part of the compound? Or does the target molecule bind or interact with the compound"?

22. Claim 6 is indefinite in reciting improper overlapping Markush groups, such that the scope of the claim is unclear. Furthermore, it is unclear due the grammatical structure of the claim whether the clause "in combination with database searching" is meant to apply to all of the recited members of the Markush group, or alternatively only to the last member. In addition, the lack of an "and" or "or" conjunction concluding the Markush group also presents confusion.

23. Claim 7 recites the limitations "the determination of the number of free amino groups in the target peptides", "the cleavage specificity of the protease used to generate the protein peptide mixture" and "the grand average of the hydropathicity of the target proteins". There is insufficient antecedent basis for these limitations in the claims.

Furthermore, Claim 7 is vague and indefinite in reciting,

> wherein the measurement of the mass of the peptides in the identifying step is further combined with (a) the determination of the number of free amino groups in the target peptides, (b) the cleavage specificity of the protease used to generate the protein peptide mixture; and (c) the grand average of the hydropathicity of the target peptides

In addition to the ambiguity raised by the lack of antecedent basis for elements (a)-(c) discussed above, Applicant's intended meaning here is not clear. In particular, it is unclear in

what sense the identification of peptide mass could be "combined" with the elements that follow. Does Applicant intend that in the case of (a), both the masses as well as the number of free amino groups in the peptides are determined? Element (b) refers to cleavage specificity of a protease. It is unclear how a protease's cleavage specificity, which does not clearly invoke any process steps or physical elements, could be "combined" with a step of measuring the mass of a peptide. Clarification is needed. Similarly, it is unclear in what sense a peptide's hydrophopthicity, which reflects a fundamental physical property of the peptide, could be "combined" with a step of measuring the peptide's mass. Clarification is needed.

Claim Rejections - 35 USC § 102

24. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

25. Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Cruickshank et al. ("Diagonal Chromatography for the Selective Purification of Tyrosyl Peptides", Canadian Journal of Biochemistry (1974) 52, 1013-17, of record).

Cruickshank et al. teach a method to isolate tyrosyl- or histidyl-containing peptides, comprising the steps of (a) adding a compound comprising a functional group that can be specifically altered (1-fluoro-2,4-dinitrobenzene, FDNB) to a complex mixture of molecules (carboxymethylated protein samples mixed with urea and other chemicals; see page 1014, right column) to form a compound-target complex (O-DNP-tyrosyl and DNP-histidyl-derivatized

proteins, which are formed as a result of the reaction of FDNB with tyrosyl side chains to give the DNP group), (b) separating the resulting mixture by paper chromatography, (c) chemically altering the DNP compound by thiolysis, and (d) isolating at least one target molecule (tyrosine and/or histidyl-containing peptides) after DNP thiolysis by paper chromatography and final purification by electrophoresis. See entire selection, in particular the abstract; page 1013, right column to page 1015, right column, first paragraph; Figures 1-2; and page 1016, the paragraph bridging the left and right columns. With respect to claim 5, the reference teaches identifying the sequence of isolated tyrosyl-containing peptides (page 1015, right column; and Table 1).

26. Claims 1-2 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Creighton, T.E. ("Proteins: Structures and Molecular Properties" Second Edition, W.H. Freeman and Company, New York, 1993), page 41).

Creighton teaches diagonal techniques for the purification of proteins, in which peptides in a peptide mixture that contain a particular amino acid are selectively isolated in two electrophoretic or chromatographic steps, which are performed with an intervening step modification step that alters the mobilities of modified peptides. Specifically, the reference teaches (a) adding a compound (iodoacetic acid) to a complex mixture of peptides, wherein the iodoacetic acid covalently modifies cysteine residues to form carboxymethyl-Cys residues (see entire selection). The reference further teaches (b) performing a first separation step, which may be performed electrophoresis or by the more common HPLC analysis (page 41, right column, the second full paragraph; and left column, the first full paragraph). Subsequently, fractions are (c) modified with performic acid, which chemically alters the carboxymethyl-Cys residues to the

sulfones (Eq. 1.84). When the peptides are (d) subjected to the same procedure a second time, modified peptides will be isolated as they lie off the diagonal (see left column, the second full paragraph).

Similar techniques can also be performed for chemical modification of other amino acids (page 41, right column).

Claim Rejections - 35 USC § 103

27. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

28. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

29. Claims 2-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cruickshank et al.

Cruickshank et al. is as discussed above. The reference teaches contacting a compound (FDNB) with a complex mixture that includes carboxymethylated protein. See especially page

1014, "Carboxylation and Dinitrophenylation of Protein". Subsequently, the DNP-adducted protein is cleaved into fragments prior to chromatography (see especially pages 1014-1015, "Treatment of CM-Chymotrypsinogen and CM-Lysozyme". As a result of this proteolytic cleavage step, a "protein peptide mixture" is formed that is comprised of the peptide cleavage products.

However, this method differs from that of the instant claims because the "complex mixture of proteins" is only formed *after* addition of the compound FDNB. As such, the compound is not added to the "protein peptide mixture" (proteolytically cleaved protein) but to the protein *per se* prior to cleavage.

The Courts have ruled that the selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results. See MPEP 2144.04.

In the instant case, it would have been obvious to one of ordinary skill in the art at the time of the invention to perform the proteolytic cleavage step prior to addition of the compound FDNB in the method of Cruickshank et al. because selection of any order of performing process steps constitute obvious variations of parameters and procedures that are routinely varied in the art. In this manner, one would arrive at the claimed invention because the proteolytically cleaved proteins would constitute a "protein peptide mixture" of fragments that would then be contacted with the FDNB.

30. Claims 2-4 and 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cruickshank et al. in view of Aebersold et al. (US 6,670,194) and Johansson et al. (US 6,716,589).

Cruickshank et al. is as discussed above. The reference differs from the invention of claims 2-4 as discussed immediately above. With respect to claims 6-7, Cruickshank et al. teach subsequent identification of the targets (tyrosyl- or histidyl-containing peptides) by amino acid analysis (page 1015, right column), but fail to specifically teach identification by measuring the mass of the peptides in combination with database searching.

Aebersold et al. mass spectrometry-based methods for characterizing isolated peptides (the abstract). The reference teaches analysis of complex mixtures of proteins, i.e., those containing 5 or more distinct proteins or protein functions, digesting the protein sample with proteases to produce peptide fragments (column 3, lines 39-68; column 5, lines 33-60; column 12, lines 44-52). By isolating and analyzing the isolated peptide fragments, the presence of protein(s) in the sample can be determined since the peptides are characteristic of the originating protein (column 3, lines 39-68).

With respect to claim 3, Aebersold et al. also teach adding an affinity labeled reagent, which selectively reacts with certain groups that are typically found in proteins (e.g., sulfhydryl, amino, carboxy groups) (see column 5, lines 33-60). Such labeled reagents are added to the complex protein mixture, which is then cleaved into peptide fragments; peptide fragments that are labeled are then isolated and identified (ibid). This is analogous to the teachings in Cruickshank in which the affinity labeled reagent FDNB is added to the protein samples prior to their proteolytic cleavage (page 1014).

Aebersold et al. further teach "multiplexing", or analysis of multiple samples in a single analysis (see column 6, lines 40-45; column 7, lines 37-42). For example, sequence identification

of multiple peptide components of a protein mixture can be obtained in a single analysis (see also heading to Table 2).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to perform the method of Cruickshank et al. using a complex mixture of proteins as taught by Aebersold et al. (rather than a single protein) because Aebersold et al. taught that sequence identification of multiple peptide components can be obtained in a single analysis (such as that of Cruickshank et al.), thus providing an advantage by allowing for multiplexing, i.e. simultaneous analysis of multiple proteins at the same time. One would be motivated to do this in order to determine the presence of a protein or proteins in a complex mixture.

Also with respect to claim 3, Cruickshank et al. exemplify addition of the labeling reagent FDNB prior to proteolytic cleavage (page 1014, right column). Aebersold et al. also teach adding labeling reagents prior to proteolytic cleavage (column 5, lines 33-46). Therefore, when performing the method of Cruickshank et al. and Aebersold et al. on a complex mixture of proteins, it would have been further obvious to one of ordinary skill in the art at the time of the invention cleave the protein after reaction with the labeling reagent FDNB.

With respect to claims 6-7, Aebersold et al. teach that protein analysis has been revolutionized by the development of powerful mass spectrometric methods and the development of computer algorithms which correlate protein and peptide mass spectral data with sequence databases and thus rapidly and conclusively identify proteins (column 1, line 60 to column 2, line 8). Such methods can determine both the quantity and the sequence identity of tagged peptides. In particular, the sequence of isolated peptides in a complex mixture can be

determined using tandem spectrometry techniques, and by application of sequence database searching techniques. Since the isolated peptide fragments are characteristic of the presence of the protein from which the sequenced peptide originated, in this manner the originating protein can be identified and thus the presence of the protein in the complex mixture determined. See column 3, lines 39-68 and column 12, line 62 to column 13, line 25.

Johansson et al. also teach that as compared with amino acid analysis (the method used by Cruickshank et al.), mass spectrometry is more sensitive (column 11, lines 54-57).

Therefore, when performing the method of Cruickshank et al. and Aebersold et al., it would have been further obvious to one of ordinary skill in the art at the time of the invention to employ mass spectrometry (which is a mass measurement method) in combination with sequence database searching as taught by Aebersold et al. in place of the amino acid analysis method of Cruickshank et al.

One of ordinary skill in the art at the time of the invention would have been motivated to do this in order to identify the protein from which the sequenced peptide fragment originated, thereby allowing the presence of that protein in the mixture to be determined.

In particular, one would be motivated to substitute more recently-developed mass spectrometry-based techniques as taught by Aebersold et al. for the older methodology of amino acid analysis in order to achieve the same purpose, namely of determining the sequence identity of the tyrosine and/or histidyl-containing peptides. The teachings of Johansson et al. also establish that mass spectrometry was recognized in the art to be more sensitive than amino acid analysis.

One of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success because Aebersold et al. teaches that the mass spectrometric methods can identify the sequences of isolated and/or tagged peptides, which describes the tyrosyl- and histidyl-containing peptides that were identified in the method of Cruickshank et al.

With respect to claim 7, the method may be said to be "based on the knowledge about the cleavage specificity of the protease" since Cruickshank et al. teach that the proteases employed (pepsin, thermolysin, and elastase) cleaved the target proteins chymotrypsinogen and lysozyme. As such, given the broadest reasonable interpretation the methods may be said to be "based on" the knowledge that these proteases cleave the target proteins.

31. Claims 2-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Creighton in view of Aebersold et al.

Creighton is as discussed above, which teaches a method substantially as claimed wherein peptides are purified from peptide mixtures.

The reference differs from the claimed invention of claim 3 with respect to the type of sample on which the method is performed. Specifically, Creighton fails to specifically teach adding the compound to a complex protein mixture that is then *cleaved* into a protein peptide mixture prior to separation step (b). Rather, in Creighton the compound is added to a protein peptide mixture; there is no specific teaching of a step in which the peptides are initially obtained by cleavage of proteins.

The reference also fails to specifically teach *identifying* the target peptides as in claims 5-7.

Aebersold et al. is as discussed above. The reference teaches that analysis of complex mixtures of proteins, i.e., those containing 5 or more distinct proteins or protein functions, can be achieved by analyzing isolated peptide fragments obtained by digestion or cleavage of the proteins in the sample mixture, typically with trypsin. See column 3, lines 39-68; and column 12, lines 44-53. This allows for "multiplexing", or analysis of multiple samples in a single analysis (see column 6, lines 40-45; column 7, lines 37-42). For example, sequence identification of multiple peptide components of a protein mixture can be obtained in a single analysis (see also heading to Table 2).

Since the resulting peptide fragments are characteristic of the presence of the protein from which they originated, isolation and characterization of the peptide fragments can be used to determine the presence of the protein in the complex mixture (see also the abstract).

Therefore, with respect to claims 2-3, it would have been obvious to one of ordinary skill in the art at the time the invention was made perform the peptide purification method of Creighton on a sample that is a complex protein mixture, and to subsequently cleave the protein mixture into the peptide mixture from which peptides are isolated, in order to determine the presence of protein(s) in a complex mixture by purifying peptides obtained by protein digestion of the mixture. Motivation to modify the reference teachings in this manner comes from the teachings of Aebersold et al. that isolated peptide fragments can be used to identify the presence of the presence of the protein from which the peptides originated.

With respect to claim 3, Aebersold et al. also teach adding an affinity labeled reagent, which selectively reacts with certain groups that are typically found in proteins (e.g., sulfhydryl, amino, carboxy groups) (see column 5, lines 33-60). Such labeled reagents are added to the

complex protein mixture, which is then cleaved into peptide fragments; peptide fragments that are labeled are then isolated and identified (ibid). The affinity labeled reagent of Aebersold et al., (which may react with sulfhydryl groups) is highly analogous to the iodoacetic acid modifying reagent of Creighton et al. that reacts with cysteine residues.

Therefore, it would have been further obvious to one of ordinary skill in the art at the time of the instant invention to add iodoacetic acid to the complex protein mixture and then cleave the protein mixture into a protein peptide mixture prior to separation when performing the method of Creighton and Aebersold et al. because Aebersold et al. exemplifies this order of performing the steps when analyzing a complex protein mixture sample. Furthermore, the Courts have ruled that the selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results. See MPEP 2144.04.

With respect to claims 5-7, Aebersold et al. teach that isolated peptides can be characterized by mass spectrometric techniques: in particular, the sequence of isolated peptides can be determined using tandem MS techniques, and by application of sequence database searching techniques, the protein from which the sequenced peptide can be identified (column 3, lines 54-60).

Therefore, when performing the peptide isolation method of Creighton on a complex protein mixture in order to identify proteins in the mixture according (as taught by Aebersold et al.), it would have been further obvious to one of ordinary skill in the art at the time of the instant invention to identify the isolated peptides by mass spectrometry in combination with sequence database searching as taught by Aebersold et al. because Aebersold et al. taught that isolated peptides can be sequenced and characterized by mass spectrometry in this manner, thereby

allowing identification of the protein from which they originate, and consequently allowing for determination of the presence of that protein in the complex mixture.

With respect to claim 7, Aebersold et al. teach the protease trypsin for protein digestion (column 12, lines 44-53). It is implicit from this teaching that trypsin is known to cleave proteins. Therefore, when employing trypsin to produce the peptide fragments according to the method of Creighton and Aebersold et al., such a method would be said to take into account the "knowledge about the cleavage specificity of the protease" given the broadest reasonable interpretation of this terminology.

Response to Arguments

32. Applicant's arguments, filed 2/22/08, have been fully considered.

33. With respect to the rejection of claim 1 under § 112, 2nd paragraph in regards to the terminology "at least one target molecule **of a compound**", it appears that Applicant acquiesces with the grounds of rejection as the Reply does not include arguments specifically traversing the rejections, but merely states that the rejection has been obviated by the amendments (Reply, page 9). However, this terminology still appears in the claims as amended. Accordingly, the rejection is maintained for reasons of record.

34. Similarly, regarding the rejections of claims 7-8 under § 112, 2nd paragraph, it appears that Applicant acquiesces with the grounds of rejection as the Reply does not include arguments specifically traversing the rejections, but merely states that the rejection has been obviated by the amendments (Reply, page 9). However, the terminology at issue still appears in claims 6-7 as amended. Accordingly, the rejection is maintained for reasons of record.

35. With respect to the rejections of claims 1-2 and 6 under 35 U.S.C. 102(b) as being anticipated by Cruickshank et al. (now applied to claims 1 and 5 above), Applicant's arguments have been fully considered but are not persuasive. Applicant argues that Cruickshank et al. does not teach separating into multiple fractions as in step (b) of claim 1 (Reply, paragraph bridging pages 9-10). This is not found persuasive because it is evident in Figures 1-2 of Cruickshank et al. that in the initial separation by paper chromatography (before thiolysis), there was chromatographic separation of the sample into multiple discrete regions of the paper, e.g. off-diagonal spots or differently-migrating regions along the diagonal. These discrete regions would be considered "fractions" in that they represent different portions or fractions of the sample.

36. With respect to the rejections of claims 1-3 and 5 under 35 U.S.C. 102(b) as being anticipated by Creighton et al. (now applied to claims 1-2 and 4 above), Applicant similarly argues that the reference does not teach separating into multiple fractions as in step (b) of claim 1 (Reply, page 10). This is not found persuasive because Creighton et al. clearly teach that in so-called "diagonal" techniques involving two-dimensional separation, a mixture of peptides is first *separated* in a first dimension based on differing mobilities of the peptides, so as to form a diagonal (page 41, left column, second paragraph). Since different peptides occupy different positions along the diagonal as a result of their different mobilities, it is implicit from this that the sample has been fractionated into multiple fractions or regions along the diagonal that contain different peptides. See also discussion of the diagonal chromatography techniques of Cruickshank et al. above.

In addition, Creighton et al. also discuss "diagonal" techniques that employ HPLC rather than two-dimensional separation, which results in the generation of "many fractions" (page 41, right column).

37. With respect to the rejection of claim 3 under 103(a) as being unpatentable over Cruickshank et al. in view of Aebersold et al. (the limitations of previous claim 4 have now been introduced into claim 3), Applicant argues that one of ordinary skill in the art would not have combined the reference teachings because Cruickshank works with one protein while Aebersold et al. work with many proteins but does not use two identical chromatographic steps (Reply, paragraph bridging pages 10-11).

Applicant's arguments are not persuasive because they amount to a piecemeal analysis of the prior art teachings. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Although it is acknowledged that Cruickshank only studied one protein at a time, the teachings of Aebersold et al. establish that the prior art recognized the advantage of "multiplexing" in that multiple samples could be analyzed together in parallel.

Furthermore, as to the argument that Aebersold et al. does not teach two identical chromatographic steps, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the

test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

38. Applicant further argues that one of ordinary skill in the art will understand that operation of the method of claim 1 "unexpectedly worked" with a complex mixture of molecules (Reply, page 11). Applicant's remarks are not fully understood; it is unclear whether Applicant intends that others tried and failed to produce the claimed invention, or alternatively whether there is evidence of unexpected results.

In any event, the arguments of counsel alone are insufficient as they are not accompanied by appropriate documentary evidence or clear scientific reasoning. Applicant is reminded that whether evidence shows unexpected results is a question of *fact* and the party asserting unexpected results has the burden of proving that the results are unexpected. In re Geisler, 116 F.3d 1465, 1469-70, 43 USPQ2d 1362, 1364-5 (Fed. Cir. 1997). The evidence must be (1) commensurate in scope with the claimed subject matter, In re Clemens, 622 F.2d 1019, 1035, 206 USPQ 289, 296 (CCPA 1980), (2) show what was expected, to "properly evaluate whether a … property was unexpected", and (3) compare to the closest prior art. Pfizer v. Apotex, 480 F.3d 1348, 1370-71, 82 USPQ2d 1321, 1338 (Fed. Cir. 2007). The burden of demonstrating unexpected results rests on the party asserting them, and "it is not enough to show that results are obtained which differ from those obtained in the prior art: that difference must be shown to be an unexpected difference." In re Klosak, 455 F.2d 1077, 1080 (CCPA 1972).

Conclusion

39. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

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/Christine Foster/
Examiner, Art Unit 1641

/Long V Le/
Supervisory Patent Examiner, Art Unit 1641